SYNTHESIS OF TOBACCO ADDITIVES

Jeffrey I. Seeman

1000414742

Source: https://www.industrydocuments.ucsf.edu/docs/zhnb0000

THIS REPORT IS CONFIDENTIAL TO THE BUSINESS OF THE COMPANY: IT SHOULD BE CAREFULLY HANDLED, IS NOT TRANSFERABLE TO ANOTHER INDIVIDUAL, AND IS NOT TO BE PHOTOCOPIED.

If the report has served its purpose and is no longer needed, please return it immediately to the Central File at the Research Center for record keeping purposes and destruction.

Accession Number: 83-121

Copy Number:

Issued To:

PHILIP MORRIS U.S.A.

RESEARCH CENTER

RICHMOND, VIRGINIA

CHARGE NO. & TITLE: 2500

TYPE REPORT: (X) ANNUAL ( ) SEMIANNUAL ( ) COMPLETION ( ) SPECIAL

DATE: June 16, 1983 PERIOD COVERED: April 1982 - May 1983

REPORT TITLE:

SYNTHESIS OF TOBACCO ADDITIVES

BY Jeffrey I. Seeman
Jeffrey I. Seeman

APPROVED BY Edward B. Sanders
Edward B. Sanders

DISTRIBUTION:

M. Hausermann	J. L. Charles	J. E. Wickham	A. I. Palmer
R. B. Seligman	F. L. Daylor	W. F. Claflin	T. T. Goodale
F. E. Resnik	P. N. Gauvin	W. L. Dunn	H. Gaisch
W. A. Farone	A. J. Kassman	R. Fagan	S. Hutcheson
L. F. Meyer	D. B. Knudson	R. M. Ikeda	M. Bourlas
T. S. Osdene	B. J. Kosakowski	R. D. Carpenter	F. Will
R. N. Thomson	W. F. Kuhn	R. Jenkins	W. Gannon
L. R. Turano	W. F. Mutter	A. Kallianos	E. B. Fischer
P. A. Eichorn	F. M. Watson	G. Keritsis	A. C. Lilly
D. A. Lowitz	R. M. Waugh	M. A. Manzelli	H. Merritt
K. S. Burns	J. F. Whidby	H. L. Spielberg	

KEYWORDS:
Abienol, β-hydroxy Esters, Cooked Flavor, DBC Bright, Flavors, Flavor Release, NOE, Nicotine Analogues, Odor Profiling, Pyrazines, Pyridines, SEL, Structure-Activity Relationship

1000414743

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

ABSTRACT

In this annual report, we describe our efforts for the preparation of new and novel tobacco flavorants and odorants and for the preparation of nicotine analogues. We have found that subjecting a variety of tobacco and non-tobacco substrates with abienol, a tobacco terpenoid, followed by exposure to sunlight, leads to a product possessing excellent subjectives. Procedures have been developed which allow the isolation of pure abienol from a moderately inexpensive source, Canadian balsam. Two components from the cooked flavor material which are used as standards for quality control have been purified and identified. Photooxygenated SEL leads to a material having improved tobacco flavor. Ammonia treatment of DBC bright followed by addition of malic acid leads to a Burley flavor imitation. Emphasis is also placed on relationships between odor and pharmacological properties and structure. These relationships serve as the basis for the choice of compounds which we synthesize. We have prepared a wide range of alkyl pyridines, pyrazines, pyrimidines, quinolines and other aromatics for subjective studies. These substances will serve as the odor stimuli in a number of subjective studies aimed at relating chemical structure and physiochemical properties with odor. More thorough analyses of the Boelens odor profiling data bases have been performed and physiochemical parameters have been obtained and correlated with the odor groupings.

Molecular mechanics algorithms were used to predict the ground state minimum energy conformation and strain energies (SE) for a series of hydroxy esters prepared by Y. Houminer as flavor

1000414744

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

release agents; the SE were found to correlate excellently with pyrolysis rates.

We have completed the synthesis of large quantities of optically pure (-)-nornicotine and (+)-nornicotine. We have synthesized optically pure 6-hydroxyalkyl- and 6-alkylnicotinoids. Also prepared are series of N'-alkylaminonornicotines, anabasine analogues, substituted and unsubstituted aminoalkylpyridines, and 6-chloromethylnicotine. Studies involving conformational analysis and nitrogen accessibility were performed.

The rates of extraction of salts from tobacco dust were determined using conductometric techniques.

1000414745

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

I. INTRODUCTION

This report summarizes the accomplishments of Charge No. 2500 personnel listed below:

J. I. Seeman (Project Leader)

C. G. Chavdarian (separated from Philip Morris July, 1982)

L. E. Clawson (separated from Philip Morris August, 1982)

Y. Dragan (joined project November, 1982)

H. V. Secor

T. Katz (joined project May, 1982)

R. Southwick

K. McCourt (co-op student, Georgia Tech)

M. Sito (co-op student, Virginia Tech)

The effort in this project is divided into two distinct areas of research: tobacco flavorant technology[1-8] and nicotine and tobacco alkaloid chemistry and pharmacology.[1,6,7,9] There are basic, fundamental similarities in the goals of these two programs. In both cases, we are dealing with substances which can interact with living organisms eliciting some particular response(s).

With regard to tobacco flavorants, we are interested in the odor and flavor of specific tobacco constituents and related compounds. When we deal with nicotinoids, we may be interested in peripheral or central nervous system properties or perhaps the response of a particular compound on an isolated system, e.g., guinea pig ileum.

We have detailed the nature of the commonalities between the flavor/odor program and the nicotine program in the 1981-1982

1000414246

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

Annual Report of this project,[10] along with a very detailed though generalized discussion regarding the nature of structure-activity relationships.[11] The multidisciplinary character of these programs is evidenced by inspection of Table I.

Table I. Multidisciplinary Aspects of Our Programs

1. Nicotine Behavorial Testing Program: Victor DeNoble, Paul Mele.
2. External Testing Program: T. S. Osdene, Prof. Leo Abood, University of Rochester; Bob Pages, Jim Charles.
3. Tobacco Flavorant Subjective Analyses: CES; Dan Ennis, Lisa Eby, Archie Williams, and numerous panel members.
4. Analytical Studies: NMR group; Ronald Bassfield, Richard Cox, and Jan Wooten.
5. Computer Applications and Theoretical Chemistry: James Kao.
6. Physical/Theoretical Chemistry: John Schug, Jimmy Viers (VPI&SU).
7. Tobacco Field Studies: Dan Teng.

In this report, we will focus primarily on the chemical aspects of our work.

II. FLAVOR CHEMISTRY[1-8]

A. Objectives

1. To evaluate a broad base of tobacco flavor types.
2. To develop novel flavor systems.
3. To develop structure-activity relationships in flavor systems which have importance in the tobacco field.

1000147247

Source: https://www.industrydocuments.ucsf.edu/docs/zlm0000

4. To initiate work which could have impact with respect to flavors and commercial products.

5. To develop an understanding of how flavorants can contribute to low tar systems.

6. To follow-up flavor leads developed by other PM areas.

7. To develop and maintain an expertise in areas known to be important to tobacco flavor.

8. To assist Flavor Development.

9. To develop methods for the non-semantic evaluation of flavorants.

10. To understand the mechanisms of the flavor response, expecially as related to tobacco flavorants.

11. To develop a patent position in tobacco flavorants.

B. Overview of Flavor Research

To some extent, we have used the terms odorant and flavorant interchangeably. One major goal of our work is to develop an appreciation of how the chemical structure of an odorant affects its perceived odor, and by implication, its flavor. Odor properties, rather than flavor, are being studied because the experimental protocol is simpler. Furthermore, a flavorist is often guided in choice of flavorants in large part by the odor of the material. Although odor studies are seemingly simpler, nonetheless, they are still extremely complex, involving ultimately a subjective evaluation.

In order to discuss our results pertaining to the above objectives, we can classify our efforts into a number of discrete

1000414748

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

but highly interactive areas. These are (1) development of simple processes which can incorporate desirable tobacco flavors onto tobacco and/or non-tobacco smoking materials; (2) synthesis of potential flavorants/odorants; (3) development of flavor/odor-structure relationships; (4) lend support to Flavor Development where chemical expertise can have specific impact on commercial processes, e.g. cooked flavors; (5) development and on-going utilization of advanced methods of subjective analyses; (6) participation in an international program aimed at the characterization of environmental odors, and (7) isolation and identification of potentially interesting flavorants/odorants.

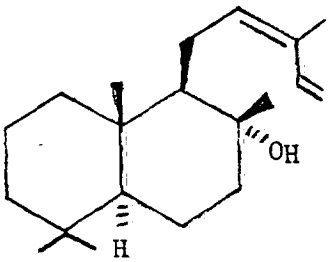
C. Development of Novel Tobacco Flavorant Processes[3,4]

One approach toward the discovery and preparation of novel tobacco odorants/flavorants and toward the reproduction of desired tobacco flavor qualities in materials lacking such qualities is based on mimicking nature. We can examine the results of oxygenations and/or photochemical reactions of tobacco materials or of pure terpenoids sprayed onto tobacco materials. In this approach, we examine gross subjective properties resulting from "unnatural" reactions and reaction mixtures which have been designed to mimic natural processes and transformations.

1. Abienol (1) is a tobacco diterpene which is present in the cuticular wax of green Oriental leaf at about 0.005% by weight. Upon curing in the traditional manner, abienol undergoes a degradation to give a wide range of products which constitute the complex woody flavor characteristic of the top grades of oriental; i.e., the leaf develops a pleasant woody aroma. The woody aroma is the result of photooxidative degradation of *cis*-abienol.

1000141749

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000



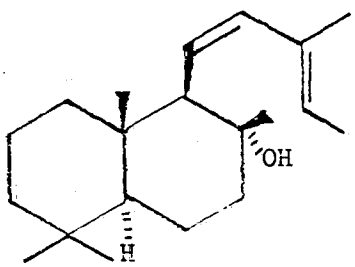
1

A process has now been developed whereby the same complex woody flavor can be attained using any filler types. Thus, when abienol is sprayed on Marlboro filler at 2% by weight and the resultant material exposed to sunlight for 6 hours, the filler acquires a pleasant woody aroma. Cigarettes made from this filler exhibit the same complex woody notes found in oriental; the sidestream smoke from these cigarettes is extremely pleasant. Bright tobacco was treated with abienol and sun cured during the summer of 1982.[12] Following a few months of storage, the tobacco gave a very distinct Izmir Oriental tobacco-like aroma which is slightly different from treating cured bright tobacco with abienol. When the filler is over-sprayed with malic acid and an oxo-hexanoic acid (CR-1719) the mainstream smoke is very similar in flavor properties to high-grade oriental; unlike oriental side-stream, however, this is universally acclaimed as very pleasant. This process offers the opportunity to eliminate our dependence on oriental leaf while providing a blend component devoid of the objectionable sidestream properties of oriental leaf.

1000414750

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

These very positive results not only encouraged us to optimize our procedures for obtaining abienol but also for developing methodology for abienol quantitative analysis. A Canadian fir balsam extract contains approximately 12% *cis*-abienol, identical in all respects to that found in tobacco. Initially, we developed an abienol isolation procedure which incorporated degassing the Canadian balsam extract, Kugelrohr distillation followed by a somewhat tedious liquid-liquid chromatography. This procedure also had the disadvantage of producing an unwanted side product, namely neoabienol (2). Neoabienol arises during the silica gel chromatography of the extract. Careful examination of base extracted Canadian balsam distillate indicates the presence of only one abienol isomer, that being abienol itself, thereby establishing that neoabienol is an artifact.



2

We have now developed a superior procedure not only in ease of operation but also in terms of purity of the resultant abienol. Molecular distillation followed by base extraction of the distil-

1000414751

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

late gives a nearly quantitative recovery of substantially pure abienol. Although abienol is unstable and will polymerize on standing, it can be stabilized in ethanolic solution containing the anti-oxidant BHT. Presently we and others at R & D are pursuing several courses of action to explore the flavor aspects of abienol: ozonolysis of abienol[13]; large scale experiments with leaf during the 1983 growing season to obtain quantities of filler for POL testing;[12] photochemical methods to convert abienol on RL; tissue culture and genetic engineering as an abienol source;[14] experiments to select plants with high abienol levels; and investigation of abienol smoke chemistry.[15]

2. Cooked Flavor Chemistry[3,16]

Among the specifications developed for quality control monitoring of batches of cooked flavors is a gas chromatographic method which measures three components in the cooked flavor mixture. To substantiate the validity of this method, the identity of these components was established.

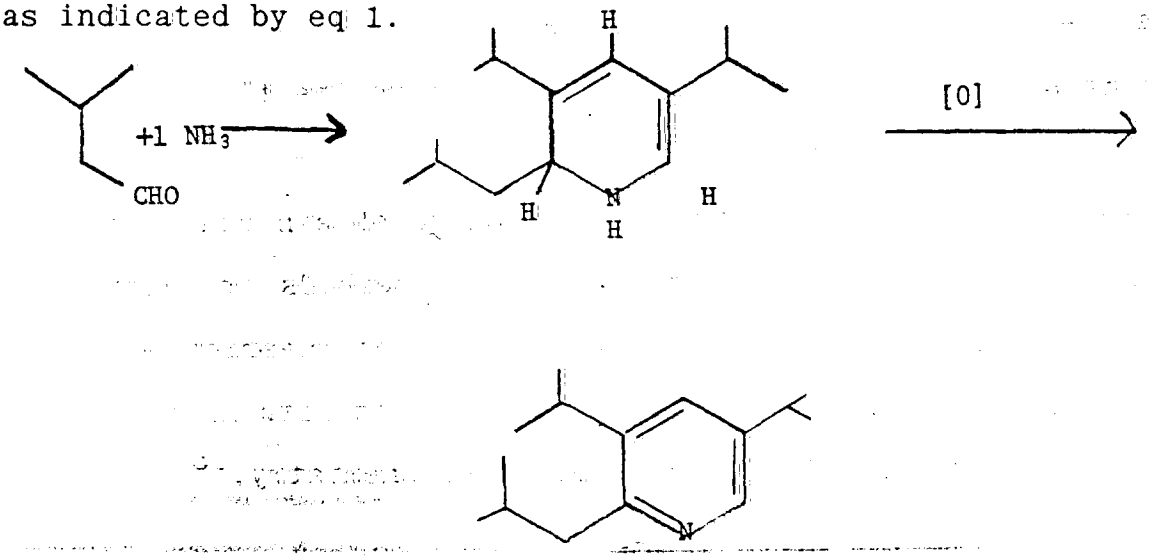
Three gallons of the cooked flavor mixture were extracted to give 1.7 g of material which was separated by distillation into two fractions. From these fractions, three individual components of particular interest (A, B and C) were isolated in sufficient quantities for spectroscopic characterization.

Component A gave a molecular ion of 219 and UV and ^1H NMR spectra which suggested a pyridine ring substituted with two isopropyl groups and one isobutyl group in positions 2, 3 and 5 of the pyridine ring. From mechanistic arguments the trimerization of isovaleraldehyde and reaction with ammonia would give

1000414752

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

2-isobutyl-3,5-diisopropylpyridine (3). This was confirmed by heating isovaleraldehyde in ammonium hydroxide. After the appropriate work-up a compound identical with component A was isolated, as indicated by eq 1.



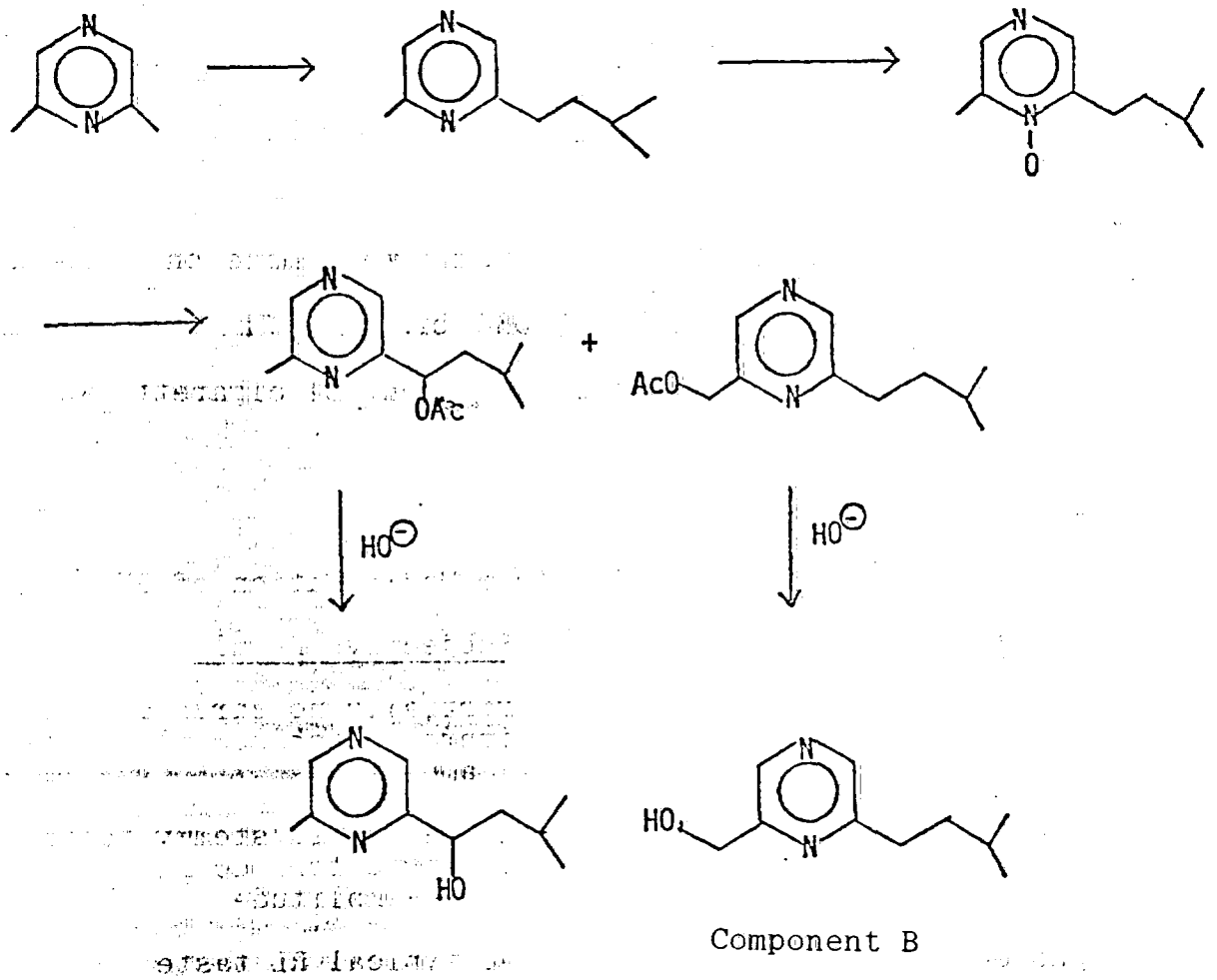
3

(component A)

Component B gave a molecular ion of 180 and IR and ^1H NMR spectra suggested a pyrazine substituted with an hydroxymethyl group and an isoamyl group. The pattern of substitution could not be determined although 2,6-substitution was strongly indicated. An authentic sample of 2-hydroxymethyl-6-isoamyl pyrazine was prepared by an unequivocal synthesis and confirmed the identity of Component B.

1000414753

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000



Component B

Component C, of molecular weight 194, is a methyl homolog of component B and was not further characterized.

3. NOD[3]

Concurrent with the investigation of process parameters for the NOD project, we began to monitor the subjective properties of the product. The initial runs were occasionally found to have a somewhat putrid odor. In an attempt to alleviate the unpleasant odor, an aliquot of de-nitrified SEL was photo-oxygenated for a

1000414754

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

period of 6 hours. Following concentration and application to RL, it was found that the subjective properties were greatly improved.

The limited subjective evaluations were made on hand-made cigarettes using 40% RL and 60% DBC bright. The subjective results are presented in Table 1. The control cigarette was made using untreated SEL.

TABLE 1. Subjective Results from Modification of SEL

Treatment	Subjective Result
photo-oxygenated SEL	virtually no cardboard taste improved tobacco flavor and amplitude
photo-oxygenated, de-nitrified SEL	no cardboard/stemmy taste improved tobacco flavor and amplitude
photo-oxygenated, filtered SEL	no typical RL taste smooth, sweet, flue-cured character

A series of experiments was carried out to determine which experimental variables were necessary to achieve the observed subjective improvement. To minimize variability the same batch of SEL was used for each experiment. Cigarettes for evaluation were prepared as described above. The results of this investigation are summarized in Table 2.

1000414755

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

TABLE 2. Experimental Parameters and Subjective Results from SEL Treatments

Treatment	Result
O_2 + light	subjective improvement
N_2 + light	no difference
N_2	no difference
O_2	subjective improvement
air	subjective improvement

These experiments clearly indicate that oxygen is the active agent in the alteration of the flavor properties.

In cooperation with Project 2106 (C. Owens) we have monitored the subjective properties of CEL from the NOD process. Oxygenation of SEL caused an improvement in the subjective response only when the feedstock was adjusted with potassium salts. All other salts used resulted in an RL sheet exhibiting the usual subjective response whether oxygenated or not. These evaluations established that the NOD process gave acceptable product which can probably be flavored with existing systems.

4. Ammonia Treatment of DBC Bright[3]

A preliminary experiment treating DBC Bright filler with liquid ammonia was carried out. Gaseous ammonia was condensed onto the filler until the filler was completely immersed in liquid ammonia (b.p. -33°C). The mixture was allowed to stand for about one hour, and the volatiles were allowed to evaporate overnight. Subjective evaluations showed good throat impact with cigar character.

1000414756

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

Analysis of this filler by FT-IR evolved gas analysis (see Figure 1) indicates that the treatment is less destructive than the CAR process and closer to the ammonia profile of burley than other ammonia treatments.

When the filler was subsequently treated with malic acid, the cigar notes disappeared and throat grab moderated. This result suggests than a reasonable imitation of burley flavor can be achieved using (a) liquid ammonia; and (b) malic acid to smooth slightly. These areas are now being pursued by Project 2106.

D. Odor/Flavor-Structure Relationships[1-3,6,7]

There is a significant void in the area of odor/flavor subjectives, namely an understanding of the relationships between subjective responses and chemical structure. This area is important to PM in that it offers us the potential of designing flavorants by rational means rather than by random selection of candidates. We have thus devoted a portion of our effort toward the basic understanding of what structural features are important contributors to odors/flavors which are of value to tobacco. We note that we pursue this topic in the framework of the tobacco field, studying classes of compounds which have been known to be important, eg. pyridines, pyrazines, pyrimidines, thiazoles, etc.

Two different but related studies have been carried out in the past year: (1) odor/structure studies of specific series of materials prepared based on tobacco flavorant leads and structural considerations; and (2) statistical analyses of odor profiling data obtained external to Philip Morris (Boelens study, Naarden).

1000414757

Source: https://www.industrydocuments.ucsf.edu/docs/zmn0000

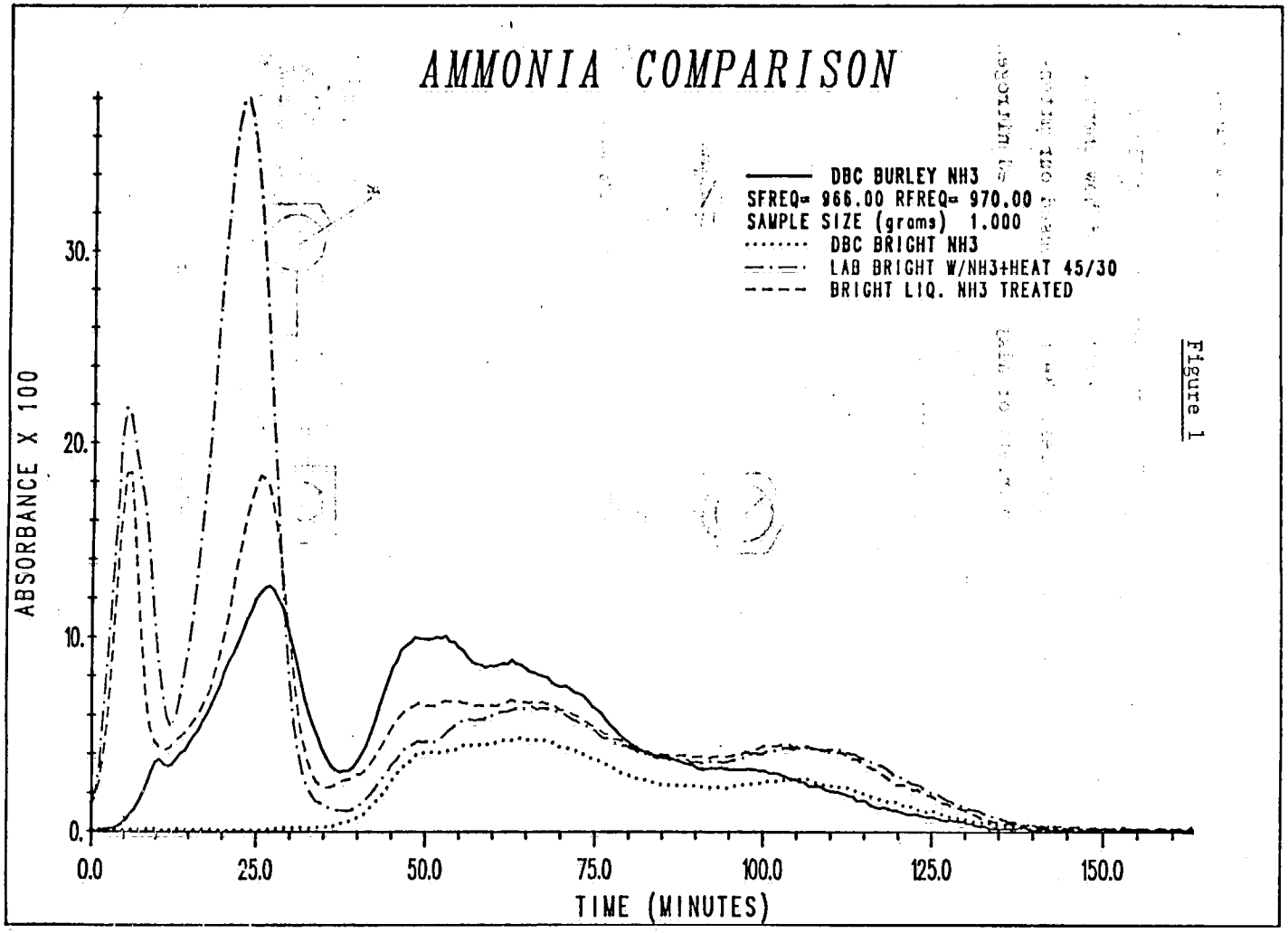


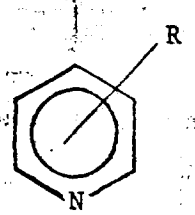
Figure 1

1000414758

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

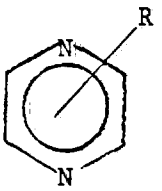
We will discuss these two approaches separately in the following sections.

1. Our major synthetic chemistry work in odor/flavor studies has been directed toward an understanding of how chemical structure determines odor properties. We have focused our attention on the preparation of a variety of alkyl substituted nitrogen heterocycles, 4-9. The selection of compounds to prepare has been governed by our previous odor studies and the investigation of cooked flavor components.



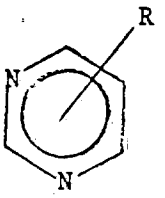
4

pyridines



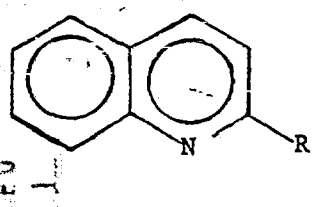
5

pyrazines



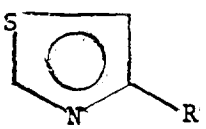
6

pyrimidines



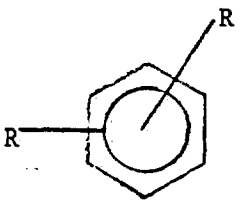
7

quinolines



8

thiazoles



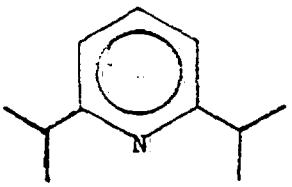
9

toluenes

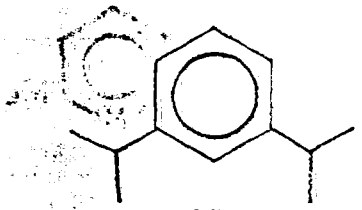
1000414759

Source: https://www.industrydocuments.ucsf.edu/docs/zlml0000

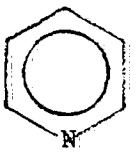
Analysis of the subjective odor data presented in our previous report[10] indicated that in each series investigated (MDS I, MDS II, and MDS III) the odor properties were dependent on nitrogen accessibility. We had noted that the odor quality of 2,6-diisopropylpyridine (10) was nearly identical to that of m-diisopropylbenzene (11). In contrast, it is well known that pyridine (12) and benzene (13) have quite different odor qualities. We postulated that nitrogen accessibility is an important factor in heterocyclic substrate odor quality. To test this hypothesis, we have now completed the preparation of a series of 2,6-dialkylpyridines 14 and m-dialkylbenzenes 15, designed such that we have a pair of substrates (a pyridine 14 and a benzene 15) having identical substitution patterns. The materials available to date are shown in Diagram I.[1,6,7]



10

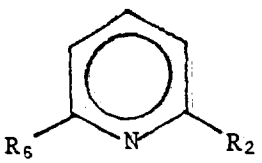


11

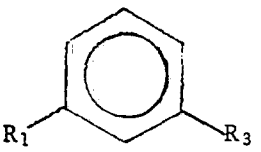


12

13



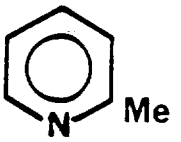
14

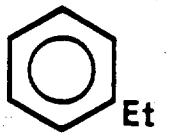


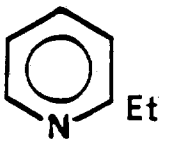
15

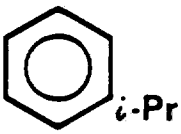
1000414760

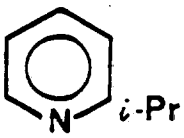
Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

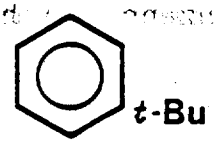


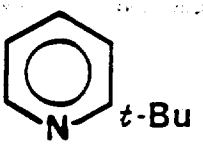


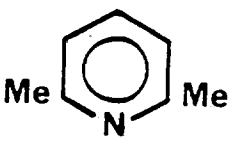


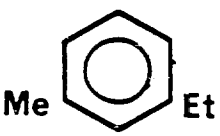


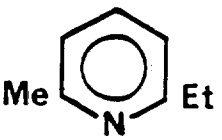


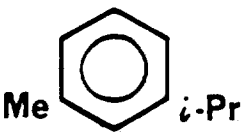


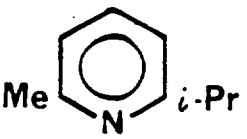


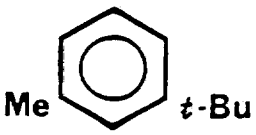


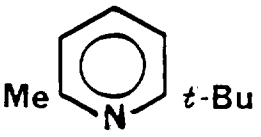






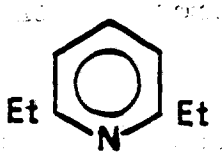


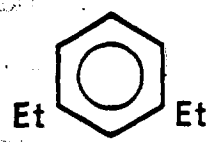


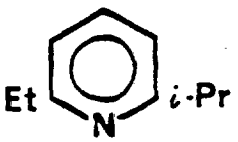


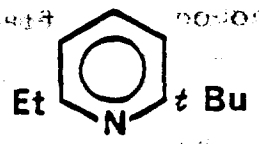
1000414791

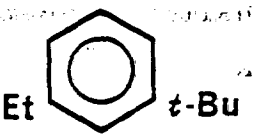
Source: https://www.industrydocuments.ucsf.edu/docs/zlm0000

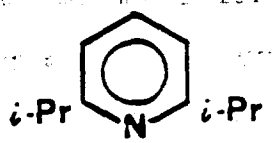


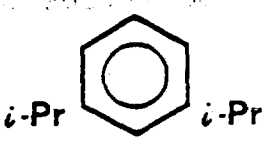


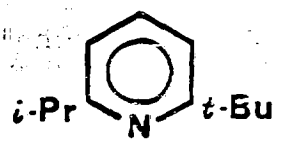


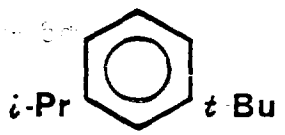


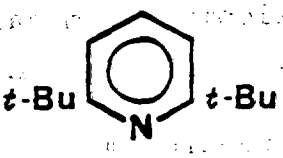


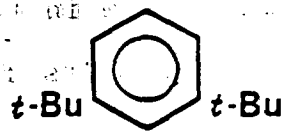












1000414762

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

As indicated in the introduction section of this report, odor-structure investigations require a multidisciplinary effort, though somewhat overlapping, having distinct responsibilities of different groups. With the first candidate series in hand, we have now organized an Odor Flavor-Structure Group which has chosen the following two goals as its initial targets:

"1) To evaluate a variety of sensory techniques, in part by comparing results using the same compounds, with a goal of defining the capabilities and limitations of the different techniques. From this research, a methodology will be chosen that will be the most appropriate and sensitive for testing in the tobacco odorant/flavorant field; and

2) To determine a structure-activity correlation for a specific series of odorants of potential value to the PM industry, incorporating, e.g., pyridines and pyrazines."[17]

D. Ennis, L. Eby, and A. Williams are currently in the process of developing and selecting candidate sensory techniques for subjective evaluation of the aromatic odorants, 14 and 15. Together with J. Kao, J. Schug (VPI) and J. Viers (VPI), we (J. Seeman and M. Sito) are in the process of developing chemical and physiochemical descriptors for this series of odorants; Table 3 lists some of the descriptors currently being generated.

1000414763

Source: https://www.industrydocuments.ucsf.edu/docs/zml0000

TABLE 3[18]

Chemical and Physiochemical Descriptors for Structure-Odor Correlations for 14-15

1. Ground State Geometries
2. Steric Hindrance Factors; Accessibility Factors.
3. Electrostatic Potentials based on Ab Initio Wave Functions
4. Experimental Partition Coefficients
5. Dipole Moments
6. Charge Densities/HOMO and LUMO
7. Molecular Surface/Molecular Volume

We have to date made significant progress in obtaining Table 3 descriptors for Diagram I-III materials, though we will not detail these results herein.

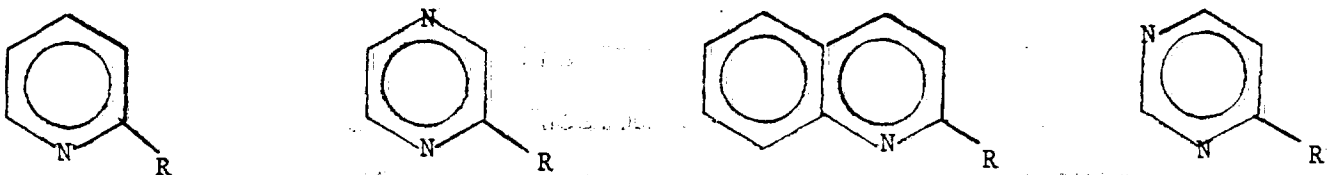
We have designed these studies such that the results obtained can then be used for the analysis of more complex subjective results for additional candidate odorants/flavorants. For example, from the investigation of cooked flavor components and observations of odor properties of alkyl pyrazines, it appears that a branched alkyl group in a position alpha to an aromatic nitrogen confers interesting odor properties on the molecule. To assess the generality of this hypothesis two additional series of alkyl substituted pyridines, pyrazines, pyrimidines and quinolines have been prepared[2] for odor studies during the coming year.

In the first series, we prepared[2] twenty-one members of a series of potential tobacco flavorants/odorants based on two specific structural features: (a) a heterocyclic ring system,

1000147694

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

either pyridine, pyrazine, quinoline, or isoquinoline; and (b) an alkyl substituent α to the ring nitrogen, including isobutyl, cyclopropylmethyl, isopentyl, and *sec*-butyl. By careful analysis of the subjective results of these materials we will be in a position to compare the relative importance of the ring and of the particular substituents. This series of compounds can be generalized by structures 16-19. The specific compounds prepared to date are shown in Diagram II.



16 17 18 19

R = C_4- and C_5- alkyl

In the second series, we examine in detail a conclusion made from previous odor-structure studies (MDS-I, MDS-II, and MDS-III); namely, that molecular weight is a crucial feature in odor quality. To neutralize the molecular weight component in odor quality, we have prepared[2] a series of pyridines shown in Diagram III having the key alkyl substitutents and possessing various degrees of nitrogen accessibility and having the same empirical formula and molecular weight. Examination of Diagram III indicates a remarkable series of interrelationships among the compounds in terms of substitution pattern and connectivity.

1000414265

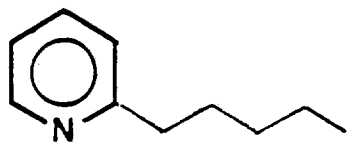
Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

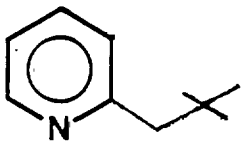
19

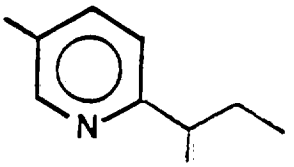
Diagram II

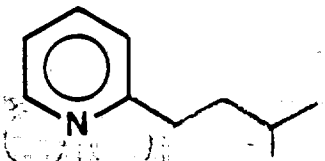
Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

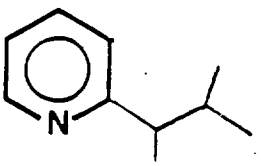
Diagram III

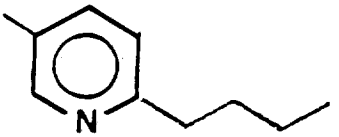


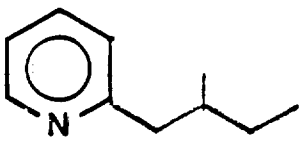


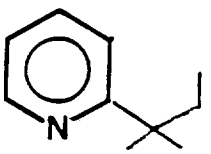


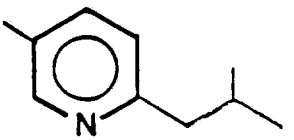


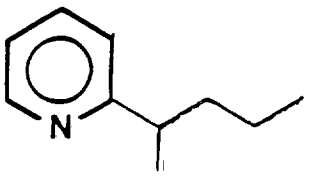


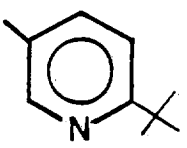












1000147267

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

2. Odor Profiling of Boelens Data

Last year, D. Ennis obtained the detailed results of a study performed by Boelens at Naarden International as part of their program in the characterization of perfume chemicals. Boelens used a set of 30 reference odorants and asked the panelist to rate each stimulus in comparison to the odor of the reference materials. He generated numerical data which did not rely on verbal descriptors. The majority of our analyses of the Naarden work was performed by D. Ennis and P. Bowman. Initial results of this project were reported in detail[19] and more statistical analyses were performed by C. Chase and T. Payne.[20]

The initial groupings determined by Bowman[19] were considered to have limitations because no minimum criteria were applied to the odor subjectives; i.e., all subjective results, including null responses, were used in the data analysis. The second generation statistical analysis incorporated a set of minimum criteria for odor subjective acceptance, and this resulted in the analysis of a much smaller set of odorants (61 in generation II, 308 in generation I). Five groups of odorants were obtained.

We consider the second generation groupings to be more reliable than the first generation groupings. However, the small number of odorants and their strong resemblance in most cases to one of the reference odorants renders the second generation procedure somewhat undesirable in terms of derivation of odor-structure relationships. We are currently examining other odor acceptance criteria, and the resultant statistical analyses, with a goal of developing reliable groupings for a larger number of stimuli.[21]

1000144768

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

We have also begun to produce chemical and physiochemical descriptors for the stimuli in the Boelens study. Thus, we have produced[2,22] connectivity indices for each of these stimuli. Connectivity indices are essentially topographical descriptions of chemical structures and have been used in numerous studies over the last ten years as correlates to a variety of types of pharmacological results. We have recently completed a study[23] which examines the relationships between connectivity indices and chemical reactivity of a number of different organic chemical processes.

We have also numericalized a number of structural and functional group features of the Boelens data.[24] This set of descriptors is very basic and unsophisticated in terms of chemical/physiochemical parameters and includes indicator variables primarily; e.g., ketone, presence of nitrogen, long chain hydrocarbon moiety, alcohol, etc. Using these 50 descriptors, discriminant analysis was performed on the entire data set, independent of the subjectives. Because the program attempts to fit the compounds into the 27 sets, the probability of random correct classification is 3.7%. Impressively, this approach correctly classified 59.7% of the odorants into the 27 groupings. We were also able to correctly classify ca. 50% in the jackknife procedure.

With regard to the Boelens odor study, which is particularly rich in a wide assortment of subjective results, we intend to: (1) determine which of the structural/functional group entities are most important and perform additional statistical procedures (e.g., factor analysis) to minimize the number of variables used,

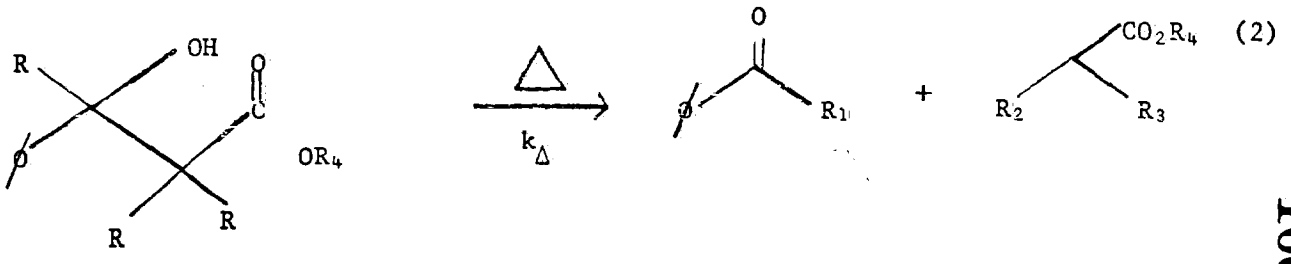
1000414769

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

(2) examine all the groupings using the connectivity indices as descriptor variables; (3) examine the stability of the groupings as a function of the subjective criteria acceptabilities chosen; and (4) correlate the most stable groupings with chemical descriptors with a goal of elucidating important chemical features in both the odor profiles and in the choice of the odor standards.

D. Theoretical Modeling of Flavor-Release Systems[7]

In collaboration with James Kao, we have begun to determine the minimum energy conformations for a series of hydroxy esters synthesized and pyrolyzed by Y. Houminer as flavor release agents. The goal of our current study is to determine if we can correlate the experimental rates of pyrolysis of these hydroxy esters to acetophenone (or benzaldehyde) and to alkyl esters (eq 2) with strain energy calculated by molecular mechanics techniques. Preliminary results for six of the eight compounds studied led to an exceptionally high correlation (r 0.9982) for compounds which pyrolyze with a rate range of over 2000. See Figure 2. These

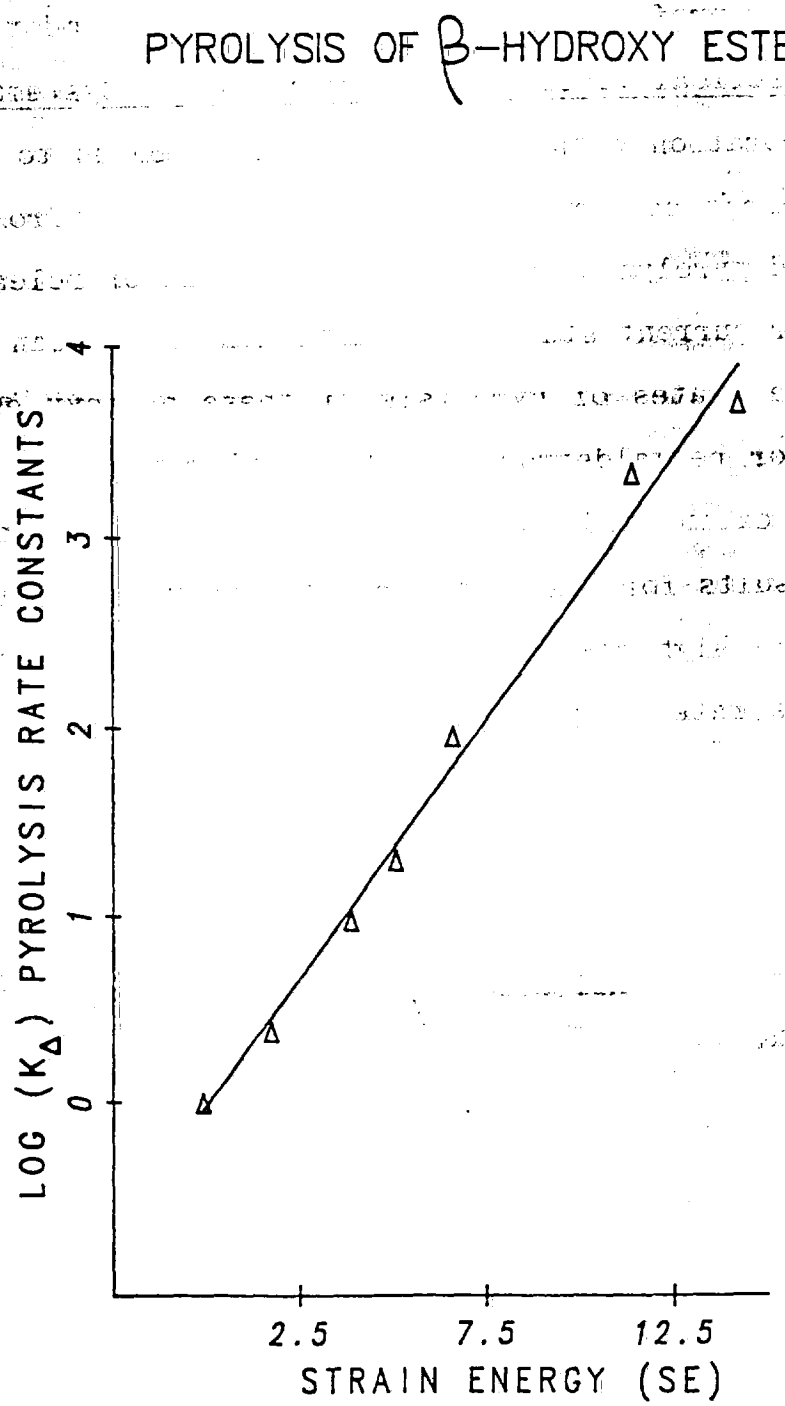


(2)

1000414720

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

Fig. 2



1000114271

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

studies may allow us to calculate pyrolysis rates of previously unknown materials to determine if they are worth preparing in the first place as potential flavor-release agents.

III. NICOTINE AND TOBACCO ALKALOID CHEMISTRY[1,6,7,9]

A. Objective

There are eleven specific objectives that are addressed by the nicotine program, and these are as follows:

1. To develop a fundamental understanding of the mechanisms by which nicotine and other tobacco alkaloids interact with peripheral and central nervous system receptors *in vitro*.
2. To determine if nicotine analogues can be designed which exhibit differential *in vivo* activity, in particular, to separate out central nervous system responses from peripheral responses.
3. To determine if nicotine analogues can be designed which exhibit differential activity at different receptors *in vitro*.
4. To develop correlations between *in vitro* systems (e.g., receptor binding) and *in vivo* tests (e.g., behavioral studies and rat blood pressure).
5. To assist the Behavioral Research group's efforts to delineate central and peripheral nicotinic effects

1000114772

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

6. To investigate the possible correlation of structural and chemical parameters with biological behavior.
7. To develop procedures to synthesize nicotine analogues and isotopically labelled nicotine analogues.
8. To perform, in a collaborative fashion, pharmacological testing of nicotine and its analogues with a goal of deriving structure-activity relationships.
9. To aid other groups with problems related to tobacco alkaloids (e.g., to develop procedures for nicotine recovery from various manufacturing residues and effluents).
10. To establish PM's state-of-the-art participation worldwide in nicotine research so that PM's results can impact on external research.

In order to achieve these objectives, effort in our group is expended primarily in the synthesis of nicotine analogues, the preparation of samples for pharmacological testing, and the study of the chemical and physiochemical properties of the analogues for derivation of SARs. In this report, we will focus attention primarily on the synthesis of the new and novel nicotinoids prepared this past year and comment here that additional quantities of previously synthesized materials were reprepared for pharmacological testing purposes. In addition, we (with R. Pages and E. B. Sanders) completed a few months ago a major tabulation of the pharmacological testing results of some one hundred nicotinoids

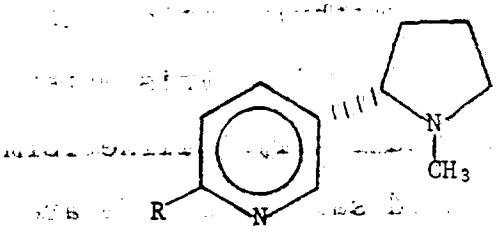
1000114773

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

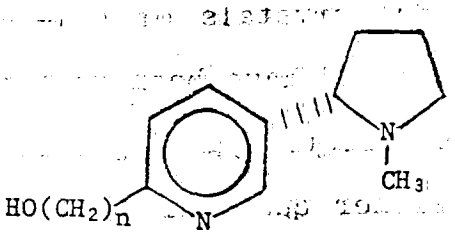
prepared by us over the years.[25] This tabulation of data has served as the basis for discussions on current progress and future directions of the nicotine analogue program.

B. Synthesis of Optically Active Nicotinoids

This year, we completed the preparation of a large number of substituted (S)-6-nicotinoids[1,6,9], including (S)-6-alkylnicotines 20 and (S)-6-hydroxyalkylnicotines 21.



20

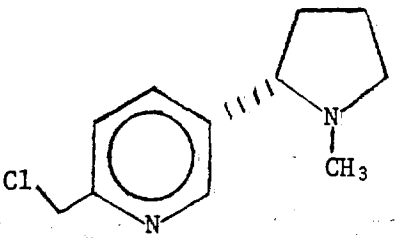


21

We also prepared[6,9] a nicotine analogue which has a reactive site on its periphery, namely (-)-6-chloromethylnicotine (22). This compound was prepared from 6-hydroxymethylnicotine and thionyl chloride. It was a stable hydrochloride salt. The material is highly reactive -- it was indeed designed to be reactive. During our attempt to purify it as a tartrate, it decomposed. This material was evaluated as a long-lasting nicotinic agent and will also be used in the receptor isolation work.

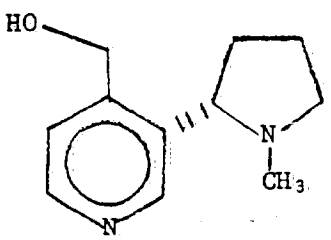
1000141724

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000



22

Beautiful crystals of (S)-(-)-4-hydroxymethylnicotine (23) were obtained and have been sent for x-ray analysis. This material is the first nicotine analogue to be obtained in crystalline form which is neither quaternized nor in its acid salt form. We are very excited about the possibility of getting structural information (bond lengths, angles and dihedral angles) from the x-ray analysis of 23.

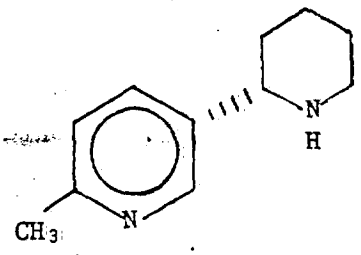


23

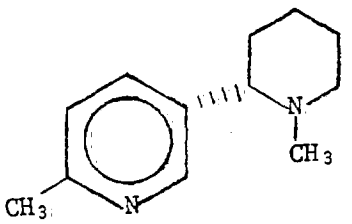
1000147225

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

Two important leads in terms of nicotine pharmacology are: (a) that 6-methylnicotine is more active than nicotine in a number of tests and possesses interesting CNS properties; and (b) that anabasine, which contains a six-membered piperidine ring and a secondary nitrogen, is active as well. We have therefore prepared[6] two nicotine analogues, 6-methylanabasine (24) and 1',6-dimethylanabasine (25) from methyl 6-methylnicotinate.



24



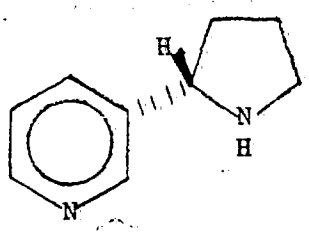
25

We have completed the first asymmetric synthesis of (-)-nornicotine (26), the natural enantiomer of the tobacco alkaloid, and (+)-nornicotine (27).[6,9] Preparative scale HPLC purifications of the diastereomers of d,l-nornicotine/menthol urethanes resulted in our obtaining ca. 500 mg quantities of the purified diastereomers. Careful acid hydrolysis of these diastereomers resulted in the isolation of (-)-nornicotine and (+)-nornicotine having the highest optical rotation observed to date for these two naturally

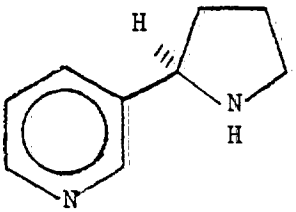
1000147276

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

occurring alkaloids. We now have in hand approximately 1 g of each of these materials which was to be used to prepare (-)-nicotine-^{3}H of very high specific activity for nicotine receptor isolation. It is also possible that this material will be for nicotine analyses via radioimmunoassay techniques.

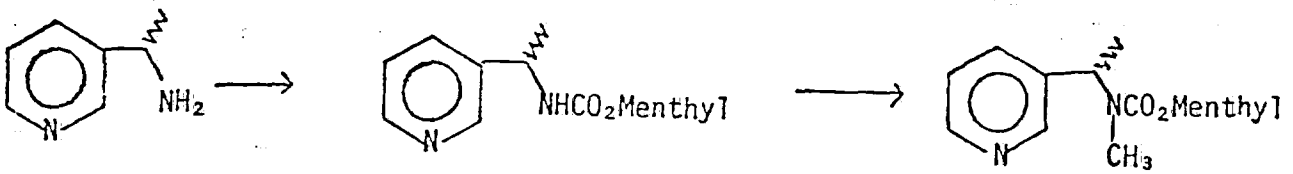


26



27

We failed in our attempt to apply our nornicotine resolution methodology to the preparation of additional optically pure nicotine analogues. The simplest potentially optically active analogue is 1-(3-pyridyl)ethylamine (28); of interest also are the related N-methylated compounds. The menthyl urethanes 29 were prepared but unfortunately, they were barely separable by HPLC. These materials were methylated to 30 in the hope that the substitution of an N-H by an N-CH_3 would improve the HPLC resolution, but unfortunately no separation was obtained.[6]

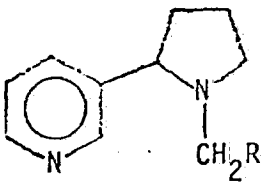


28 29 30

1000147277

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

A study assessing the conformational properties of nicotine and three of its pyrrolidine derivatives has now been completed. Though the N'-substituents of 31-33 significantly alter the pyrrolidine nitrogen electronic properties, neither careful analysis of the ^1H spectra of these compounds by Dick Cox nor *ab initio* calculations performed by James Kao revealed any conformational effects. Any pharmacological test differences will then most likely be related to basicity and lipophilicity.[7]



31, R=CH_3

32, R=CHF_2

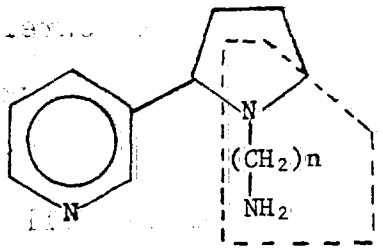
33, R=CH_3

C. Synthesis of Other Nicotine Analogues

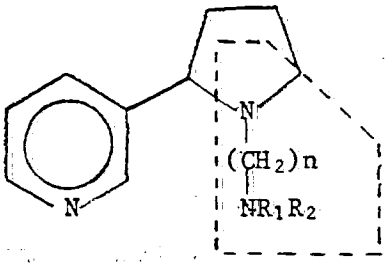
We have prepared a very large series of N'-alkylaminonornicotines, generalized by the structures 34 and 35.[6] These are of interest because of their 1,n-diaminoalkyl functionality, indicated by the dashed box in 34 and 35. Many interesting active molecules have this functionality. The compounds prepared are listed in Diagram IV.

1000147278

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000



34



35

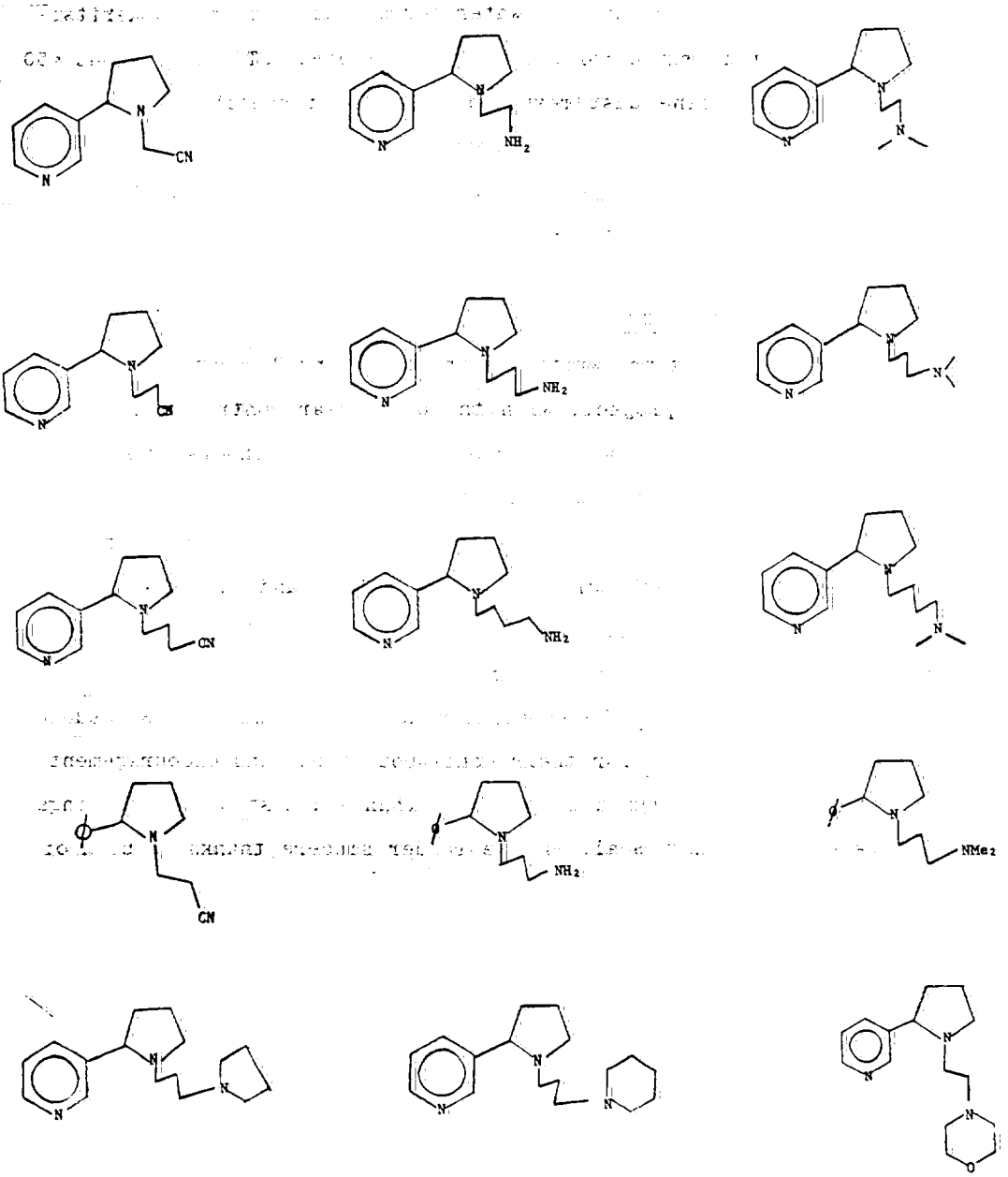
D. Miscellaneous

Over the years, we have assisted various individuals in the preparation of cigarettes having fortified nicotine levels. This generally requires preparing nicotine citrate solutions which are sprayed onto tobacco which is subsequently made into cigarettes. This year, we assisted Frank Gullotta and Jan Jones on a number of occasions and developed a relationship between nicotine loading levels on filler and cigarettes, nicotine concentration in over-spray solutions and volume.[6,7]

1000147429

Source: https://www.industrydocuments.ucsf.edu/docs/zfnl0000

Diagram IV



1000417280

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

IV. SPECIAL PROJECTS

With the invaluable contributions of Homer Hartung, we completed a study of the comparative kinetics of extraction of salts from tobacco dust by water per a request from Gus Keritsis. Extraction is rapid for both samples studied (CTII of >30 and <50 mesh). The fine dust resulted in less reproducible values of "global reaction rate constants" due to mixing properties. Nonetheless, there appears to be no statistical difference in the rates of salt extraction of the two samples.[5,7]

V. ACKNOWLEDGMENTS

This report was written with the splendid cooperation of all members of the project, with the particular contribution of R. Southwick who authored portions of the Flavor Chemistry section.

In addition to those individuals and groups whom we have cited as making major contributions to this work in Section I, we are pleased to acknowledge the assistance and cooperation of members of the Chemical Research Division, the Flavor Development Division, the Computer Applications Division, and the Analytical Research Division. We especially acknowledge Drs. T. S. Osdene and E. B. Sanders for their continuous input and encouragement. This report was typed by Anne Donathan and most of the drawings were done by Dot Seal, and we render sincere thanks to both of them.

1000414781

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

VI. 1982-1983 PUBLICATIONS AND PATENTS

1. J. W. Viers, J. C. Schug and J. I. Seeman, MINDO/3-Based Transition-State Models for the Menschutkin Reaction. Iodomethylation of Alkylpyridines, J. Am. Chem. Soc. 1982, 104, 850-851.

2. J. I. Seeman, "Smoking Compositions," U. S. Patent 4 312 367, 1982.

3. C. G. Chavdarian and J. I. Seeman, The tert-Butylation of Nicotine: Novel Reaction Pathways and Racemization Studies, Tetrahedron Lett., 1982, 2519-2522.

4. E. Southwick and H. Grubbs. "Smoking Compositions", U.S. Serial No. 373, 901, Filing Date May 3, 1982.

5. C. G. Chavdarian, J. I. Seeman and J. B. Wooten, Bridged Nicotines. Synthesis of *cis*-2,3,3a,4,5,9b-Hexahydro-1-methyl-1-H-Pyrrolo[2,3-f]Quinoline, J. Org. Chem. 1983, 105, 492-494.

6. J. I. Seeman, J. C. Schug and J. W. Viers, MINDO/3-Derived Geometries and Energies of Alkylpyridines and the Related N-Methylpyridinium Cations, J. Org. Chem., 1983, in press.

7. D. Williams, E. Southwick and Y. Houminer, "Smoking Compositions Containing Novel Acylpyrazine Flavorants", U.S. Serial No. 373, 901, Filing date May 3, 1982.

8. J. I. Seeman, The Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammett/Winstein-Holness Kinetics, Chem. Rev., 1983, 83, in press.

1000414782

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

9. J. Kao and J. I. Seeman, Conformation Analysis of Allylamine. An Ab Initio Molecular Orbital Study, J. Comp. Chem., in press.

10. J. I. Seeman, H. V. Secor, C. R. Howe, C. G. Chavdarian, and L. W. Morgan, The Radical and Organometallic Methylation of Nicotine and Nicotine N-Oxide. Reaction Pathways and Racemization Mechanisms, J. Org. Chem., in press.

11. J. C. Schug, J. W. Viers and J. I. Seeman, Reactivity Model for the Menschutkin Recation. Methylation of Alkyl- and Heterosubstituted Pyridines, submitted for publication.

12. J. I. Seeman, J. W. Viers, and J. C. Schug, The Correlation of Nonadditive Kinetic Effects with Molecular Geometries. Structure and Reactivity of Alkyl- and Cycloalkenylpyridines, submitted for publication.

13. J. I. Seeman, Recent Studies in Nicotine Chemistry, submitted for publication.

14. J. C. Schug, J. W. Viers and J. I. Seeman, Kinetic Steric Factors and Connectivity Indices, submitted for publication.

15. R. H. Cox, J. Kao, J. I. Seeman and H. V. Secor, Assessment of Isolated Electronic Effects on Conformation. NMR Analysis of Nicotine and Related Compounds and Ab Initio Studies of Model Compounds, in Manuscript Review.

16. D. Williams, E. Southwick, W. B. Edwards, "Composition of Matter and Use of Long Chain Alkyl and Alkenyl Esters of Oxocarboxylic Acids", PM 1105.

17. E. Southwick and D. Teng, "Abienol Treatment of Tobacco", PM 1129.

1000414783

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

18. Y. Houminer, D. Williams and E. Southwick, "Smoking Compositions Containing a Novel Monoacylpyrazine Flavorant", PM 1130.

19. D. Williams, E. Southwick, Y. Houminer, "Novel Pyrazine Ethers and Thioethers", PM 1146.

20. E. Southwick, "Improved Resealable Cigarette Pack", PM 1158.

21. J. Seeman, R. Pages, and J. Charles, "Selective Filtration Additives", PM 1157.

REFERENCES

1. Clawson, L. 7659.
2. Dragan, Y. 7832
3. Southwick, R. 7446, 7798
4. Katz, T. 7879
5. McCourt, K. 7571
6. Secor, H. V. 7733
7. Seeman, J. 7667
8. Sito, M. 7875
9. Chavdarian, C. G. 7594
10. Annual Report: Synthesis of Tobacco Additives, Charge No. 2500, Accession No. 82-156.
11. Special Report: Physiophysical-Physicochemical Interrelationships, Accession No. 80-177.
12. Done in collaboration with D. Teng.
13. In collaboration with B. Edwards.
14. Presently being conducted by L. Weissbecker.

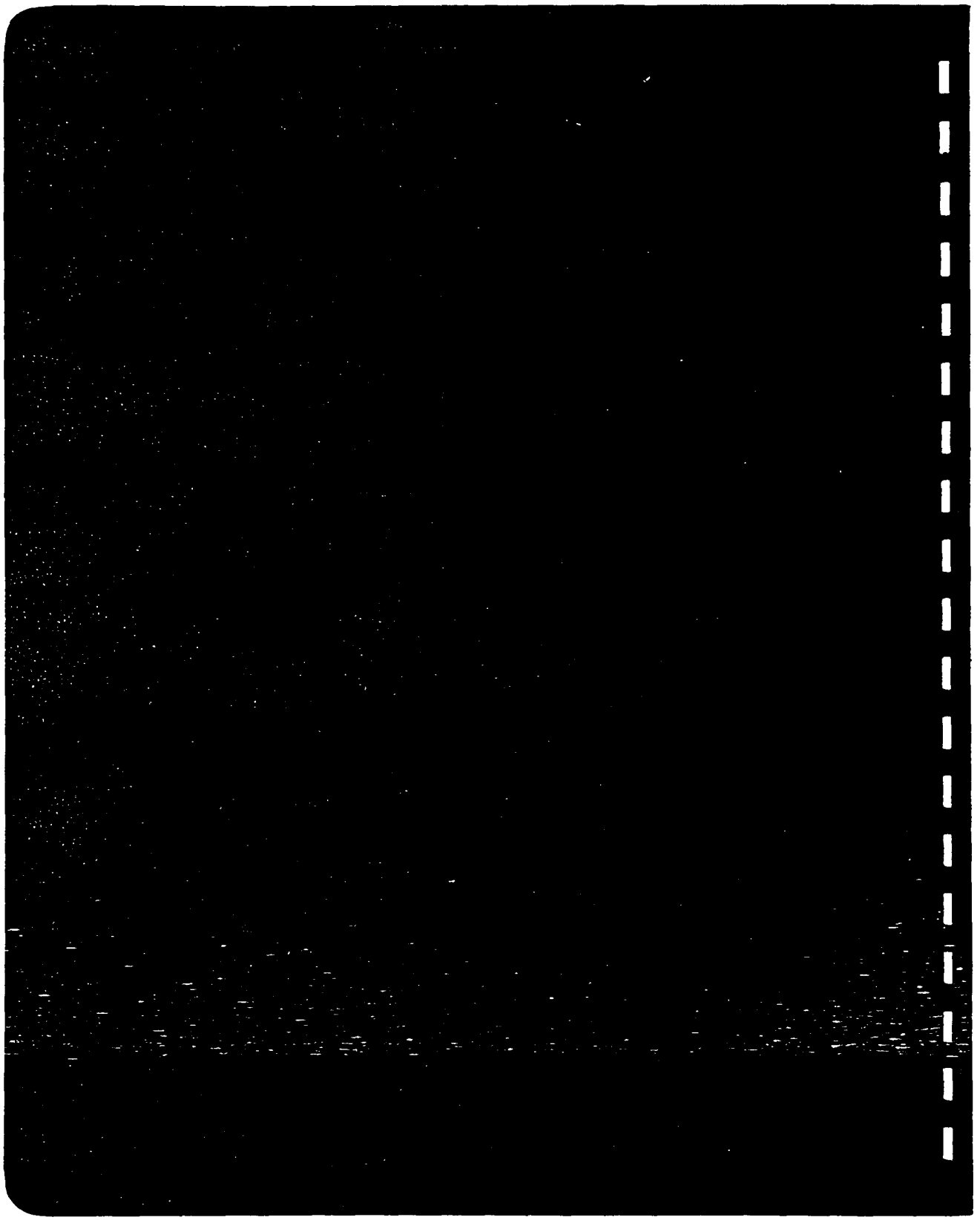
1000414784

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000

15. Presently being conducted by B. Jenkins.
16. Structural assignments made with the contributions of N. Einolf. See memo, "Structure Elucidation of Components in Cooked Flavor Volatiles", to F. Will from R. Southwick and N. Einolf, June 9, 1982.
17. Memo: "Minutes of Meeting Regarding Structure Activity Work", to Study Group from L. Eby, May 18, 1983.
18. Memo: "Sample Choice", to Study Group from R. Southwick and J. Seeman, May 18, 1983.
19. Accession No. 81-237.
20. This work was performed under the supervision of D. Ennis.
21. This is being performed by a summer intern in our project, Mr. Joseph Paulin, in collaboration with D. Ennis.
22. Connectivity indices were also determined independently by J. Schug and J. Viers (VPI) as a check for correctness.
23. J. C. Schug, J. W. Viers, and J. I. Seeman, "Kinetic Steric Factors and Connectivity Indices", submitted for publication.
24. Performed by M. Allgood, co-op student from Georgia Tech, 1982.
25. The responsibility of maintaining this tabulation has been taken over by R. Pages, whom we acknowledge with gratitude.

1000414785

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000



1000414786

Source: https://www.industrydocuments.ucsf.edu/docs/zlnl0000